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PATENT OF INDUSTRIAL INVENTION

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This patent is issued for the invention specified in the following application:

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Assignee: ATP Avant-Garde Technologies & Products S.A. Marketing & Licensing at Vacallo (Switzerland)

Representative: Riccardi, Sergio

Address: Ufficio Brevetti Riccardi & Co.
Via M. Melloni 32
20100 Milan

Title: **PROCESS FOR MANUFACTURING MEDICATED CHEWING GUM WITH PLEASANT TASTE INDEPENDENTLY OF THE ACTIVE PRINCIPLE ADDED AND CHEWING GUM TABLETS OBTAINED**

Inventor: Testa, Emilio
Maggi, Giulio Cesare

Rome, 8 July 1997

Official in Charge:
Giorgio Romani

SUMMARY OF INVENTION WITH MAIN DRAWING, DESCRIPTION AND CLAIM PROSPECT A

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D. TITLE:

PROCESS FOR MANUFACTURING MEDICATED CHEWING GUM WITH PLEASANT TASTE INDEPENDENTLY OF THE ACTIVE PRINCIPLE ADDED AND CHEWING GUM TABLETS OBTAINED

L. SUMMARY

A process is described for manufacturing medicated chewing gum exhibiting pleasant taste independently of the added active principle, characterized by the fact that the active principle is included in cyclodextrin, the mixture is dried, then mixed with the gum base and excipients for tableting and, finally, the medicated chewing gum tablet is produced directly by cold pressing. The resulting products are medicated tablets with pleasant flavor in which these active principles with poor organoleptic[1] characteristics, such as bitter flavor and other characteristics unpleasant to the patient, can be incorporated.

M. DRAWING

[1] The term organoleptic was misspelled in the Italian text. The term used there would be rendered "organoelectric", a nonsense word —Tr.

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Title: **PROCESS FOR MANUFACTURING MEDICATED CHEWING GUM WITH PLEASANT TASTE INDEPENDENTLY OF THE ACTIVE PRINCIPLE ADDED AND CHEWING GUM TABLETS OBTAINED THEREBY**

by: ATP Avant-Garde Technologies & Products S.A. Marketing & Licensing

at: Vacallo (Switzerland) Feb 2, 1995

TEXT OF THE DESCRIPTION

The invention relates to a process for manufacturing medicated chewing gum with a pleasant taste even when active principles characterized by poor organoleptic[2] characteristics are incorporated in said gum, and to the chewing gum tablets thus obtained.

In view of the popularity and wide acceptance of chewing gum, there have been attempts since the beginning of the twentieth century to incorporate pharmaceutical active principles in chewing gum, and although acceptable results have been obtained in some cases, the difficulties to be overcome have always been multiple.

These difficulties include the reproducibility of the release rate of the active substance in the gum, the degradability of the active substance during the production of the gum confections, the masking of the flavor of the active substance and numerous other factors.

To prevent degradation of the active substance, it has been possible to produce gum in the cold state, ie, by direct pressing of the ingredients.

To obtain a reproducible release rate of the active substance, microencapsulated products have been used. However, the technology is complex and the products obtained exhibit delayed release, making them poorly suited for pharmaceutical products which must be absorbed rapidly via the oral mucosa.

Hence, the problem of manufacturing a medicated chewing gum by direct pressing with instant or at least rapid release of the active principle where said gum effectively masks the specific adverse organoleptic characteristics of numerous active principles remains unresolved.

These problems are ingeniously and originally solved by the process described in Claim 1.

Indeed, although the inclusion of active pharmaceutical principles in cyclodextrin has been known for some time, there is no record in the literature of cyclodextrin ever having been used in chewing gum.

Cyclodextrins are cyclic non-reducing α-1,4-malto oligosaccharides having from 6 to 12 glucose units. There are also branched cyclodextrins whose glucose units are linked by α-1,6-glycoside linkage.

These cyclic dextrins are formed enzymatically from starch by action of glycosyl transferase produced by certain microorganisms. β-cyclodextrin having 7 glucose units and a molecular weight of 1135, and the colorless crystalline β-cyclodextrin with a purity in excess of 98% has been found to be particularly suitable.

The water-soluble or oil-soluble active principles are included in cyclodextrins and are released in the patient's mouth by action of amylase in the saliva. The technology is very simple and definitely advantageous with regard to the preparation of pellets by microencapsulation.

By including the active substances in cyclodextrins, the chemicals are stabilized and therefore rendered more soluble.

The bioavailability is thereby enhanced. In addition, the bitter taste and adverse organoleptic characteristics of many pharmaceuticals are masked in this way.

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[2] The Italian equivalent for "organoleptic" was written correctly in this sentence, confirming the earlier rendition.—Tr.

Thus, with the inventive process, one can use bad-tasting products, and generally products with sub-standard organoleptic properties by including them specifically in cyclodextrins in the manufacture of medicated chewing gum. The active principle is released from the inclusion during chewing thanks to the abundance of salivary amylase.

The procedure for obtaining medicated chewing gum is described hereinafter in a general embodiment, which is nonetheless subject to numerous alternative variants, as is evident from this text.

An amount of β-cyclodextrin is introduced into a suitable container in 1 or 2 parts of distilled water. The suspension is stirred, for example, with a mechanical stirrer, for 10-15 minutes until it is completely homogenized, and an equivalent amount of the active product is then added. The final suspension is mixed for 3-5 hr, ie, the time necessary for the inclusion of the active principle in the cyclodextrin to be completed. The water is removed under vacuum, for example, with a rotating agitator or on a stove in a water bath without exceeding a heating temperature of 50°C. A powder is obtained which can be milled and screened with an appropriate 50-500 mesh screen and is suitable for use in a tablet press. The subsequent pressing operation is preceded by the mixing of the powder obtained with 500-800 mg of gum base consisting of jelutong, gum guar and glycerin in various ratios, but usually 99/09/01. Finally, the conventional excipients suitable for obtaining tablets which provide chewing gum are added. The components used are generally carbohydrates, particularly sucrose and glucose. If non-cariogenic products are desired, the use of mannitol, sorbitol, glycocoll [sic] and the like is possible. In this case it is recommended to use sweeteners such as aspartame, cyclohexyl sulfamate, saccharin, acesulfame, and ammonium glycyrrhizinate. The use of co-adjuvants for compression, such as silicon dioxide, magnesium and calcium stearate, compritol [sic], talc and the like is frequently essential for limiting the natural tendency of the tablets to stick to the dies. Environmental conditions are also crucial for obtaining optimum chewing gums. It is appropriate to press in rooms with a temperature of less than 20°C and a relative humidity of 40-60%. The finished tablets weigh from 1.5 to 3.5 g and, when chewed, form a gummy bolus that is free of bitterness and irritating action on the mucosae. The difference in weight between individual types of chewing gum is due essentially to the different quantitative dosage of the active ingredients used, which can vary from 1 to 500 mg.

The characteristics of the inventive product will be further clarified by the following examples of embodiments, which are given solely as non-limiting examples of the scope of the invention.

Example 1

A slurry of 135 g of β-cyclodextrin and 20 g of *l*-ascorbic acid (vitamin C) in 300 mL of distilled water are placed in a glass flask equipped with a mechanical stirrer and mixed for 5 hr at ambient temperature (15-25°C). After this time has elapsed, the vacuum is applied (10-20 mm Hg), and the water removed, with progressive heating up to 50°C. The product obtained is screened on 50 mesh screen.

A portion of this product—140.5 g—is mixed with 68 g of previously prepared gum base. The preparation is done by cooling the natural gum to -10°C by milling and diluting it with 0.9% gum guar and 0.1% glycerin. The system is screened with 50 mesh screen. The mixture obtained weighs 208.5 grams. 2 g of mannitol, 2 g of glycocoll, 3 g of Syloid 254 and 1 g of Compritol are added. The system (216.5 g) is mixed for 15 min and screened through 200 mesh. 3 g of aspartame, 5.5 g of orange flavoring and 1 g of magnesium stearate are added. 226 g of granulate is obtained, which is pressed in a rotating tablet press. 90 tablets are obtained. Tablet weight: 2.5 g. Each tablet contains 200 mg of vitamin C.

Example 2

A slurry of 105 g of cyclodextrin and 15 g of paracetamol (APAP) in 250 mL of distilled water is prepared in a glass flask equipped with a mechanical stirrer and mixed for 3 hours at 25°C. After this

time has elapsed, vacuum is applied (15-20 mm Hg), and the water, gradually heated to 50°C (bath temperature), is eliminated. The product obtained is screened through 50 mesh.

A portion of this product, ie, 108 g, is mixed with 72 g of gum base, which is in turn prepared by cooling the gum base (jelutong) to -10°C, milling, adding 0.9% gum guar and 0.1% glycerin. The system is screened through 50 mesh. The finished mixture weighs 180 g.

5 g of sucrose, 3 g of Syloid 254 and 1 g of Compritol are added. The mixture is mixed in a tank at a temperature of less than 20°C. Finally, 5 g of aspartame, 3.5 g of grapefruit flavor and 1 g of magnesium stearate are added. The mixture is mixed in a tank for 5 minutes and screened through 50 mesh. 225 g of granulate is obtained and is compressed in a rotating press to obtain 90 tablets (theoretical yield). Each tablet weighs 2.5 g with a content of 150 mg of APAP (mean weight).

Example 3

A slurry is prepared from 140 g of β-cyclodextrin and 20.6 g of ibuprofen in 200 mL of distilled water. The mixture is agitated for 5 hr at 20°C (ambient temperature). The slurry is transferred to a glass flask and placed in a desiccator under vacuum and heated to 50°C. Theoretical yield: 161 g.

144.9 g is collected and mixed with 75.1 g of gum base prepared by cooling natural gum (jelutong) to -10°C, milling in a mechanical mill, adding 0.9% gum guar and 0.1% glycerin. The mixture is mixed in a tank and passed through a 50 mesh screen. The finished mixture weighs 220 g. 5 g of mannitol, 3 g of Syloid 254 and 1 g of compritol are added to it. The mixture is mixed in a tank for 20 minutes at a temperature below 20°C. Finally, 10 g of aspartame, 7.5 g of mint flavoring and 2.5 g of magnesium stearate are added to the tank stirrer. The system is mixed for 5 min, passed through a screen (50 mesh) and the finished granulate—249 g—is compressed on a rotating tablet press. 90 tablets (theoretical) are obtained weighing 2.750 g each and containing 200 mg of ibuprofen each.

Example 4

A slurry is prepared consisting of 100 g of β-cyclodextrin and 25 g of dymenhydrinate in 150 mL of distilled water. The mixture is agitated for 5 hours at 20°C (ambient temperature). The slurry is transferred to a glass flask, placed in a desiccator under vacuum and dried at 50°C until all of the water has evaporated (constant weight). The granulate is passed through 50 mesh. Theoretical yield: 125 g.

114.5 g is collected and mixed with 650 g of gum base prepared by cooling natural gum (jelutong) to -10°C, milling in a mechanical mill, and adding 0.9% gum guar and 0.1% glycerin. The mixture is mixed in a tank and passed through 50 mesh screen. The final mixture weighs 764.5 g.

350 g of mannitol, 300 g of glycocoll, 45 g of Syloid 254 and 30 g of compritol are added to the mixture. The mixture is then mixed in a tank mixer for 20 minutes. The ambient temperature must be lower than 20°C. 75.5 g of aspartame, 80 g of mint flavor and 25 g of magnesium stearate are added to the mixer. Mixing is done for 5 minutes, the material is run through a 50-mesh screen and compressed with a rotating tablet press. Yield (theoretical): 1670 g.

900 tablets weighing 1.85 g each and containing 25 mg of dimenhydrinate are obtained.

Claims

1. Process for obtaining medicated chewing gum with a pleasant flavor independently of the active principle added characterized by the fact that the active principle is included in cyclodextrin, the desiccated mixture is then mixed with gum base and the excipients for tableting and, finally, the medicated chewing gum tablet is obtained directly by cold pressing.

2. Process according to Claim 1, characterized by the fact that crystalline β-cyclodextrin is used as the cyclodextrin.

3. Process according to Claim 1, characterized by the fact that the inclusion of the active principle in the cyclodextrin is done by placing the cyclodextrin in suspension in distilled water, homogenizing the suspension with agitation, then adding the active substance, mixing the final suspension until inclusion is completed, then removing the water mechanically or by heating and milling the powder thus obtained to obtain the dried mixture for pressing.

4. Process according to Claims 1 and 3, characterized by the fact that the mixing of the powder of active principle included in cyclodextrin with the gum base is followed by the addition of the tableting excipients and co-adjuvants to prevent sticking of the tablets to the dies.

5. Process according to Claim 4, characterized by the fact that the excipients consist of carbohydrates such as sucrose and glucose.

6. Process according to Claim 4, characterized by the fact that the excipients are non-cariogenic products such as mannitol, sorbitol and glycocoll to which are added appropriate sweeteners such as aspartame, cyclohexylsulfamate, saccharin, acesulfame, or ammonium glycyrrhizinate.

7. Process according to Claim 4, characterized by the fact that the tableting co-adjuvants consist of silicon dioxide, magnesium and calcium stearate, compritol, talc and the like.

8. Process according to Claim 1, characterized by the fact that the tableting is done at an ambient temperature of less than 20°C and a relative humidity of 40-60%.

9. Medicated chewing gum tablet containing one or more active principles included in cyclodextrin mixed with the gum base composition.

10. Tablet according to Claim 9, obtained by the process according to one or more of Claims 1 through 8.

11. Tablet according to Claim 9, the finished weight of which is in the range of 1.5-3.5 g.

12. Tablet according to Claim 9, containing a dose of active principles ranging from 1 to 500 mg.

13. Tablet according to Claim 9, characterized by the fact that the active principle is *l*-ascorbic acid (vitamin C).

14. Tablet according to Claim 9, characterized by the fact that the active principle is paracetamol (APAP).

15. Tablet according to Claim 9, characterized by the fact that the active principle is ibuprofen.

16. Tablet according to Claim 9, characterized by the fact that the active principle is dimenhydrinate.

Applicant: ATP Avant-Garde Technologies & Products S.A. Marketing & Licensing

Representative: Riccardi Sergio, Industrial Property Consultant

MINISTERO DELL'INDUSTRIA DEL COMMERCIO E DELL'ARTIGIANATO

D.G.P.I - UFFICIO ITALIANO BREVETTI E MARCHI

BREVETTO PER INVENZIONE INDUSTRIALE

N. 01273487

Il presente brevetto viene concesso per l'invenzione oggetto della domanda sotto specificata:

num. domanda	anno	U.P.I.C.A.	data pres. domanda	classifica
000180	95	MILANO	02 02 1995	A23J

TITOLARE ATP AVANT-GARDE TECHNOLOGIES &
PRODUCTS S.A. MARKETING & LICENSING
A VACALLO (SVIZZERA)

RAPPR.TE RICCARDI SERGIO

INDIRIZZO UFFICIO BREVETTI RICCARDI & CO.
VIA M. MELLONI 32
20100 MILANO

TITOLO PROCEDIMENTO PER L'OTTENIMENTO DI GOMME DA MASTICARE MEDICATE DOTATE DI GUSTO GRADEVOLE INDIPENDENTEMENTE DAL PRINCIPIO ATTIVO INCORPORATO E COMPRESSE DI GOMMA DA MASTICARE COSI' OTTENUTE

INVENTORE TESTA EMILIO
MAGGI GIULIO CESARE

Roma, 8 LUGLIO 1997

IL FUNZIONARIO REGGENTE
ING. GIORGIO ROMANI

PATENTS SUMMARY

Country : Italy

Patent #: 1,273,487 A Index#: 5765

Inventor: Emilio Testa et al. Issue Date: 07/08/97

Assignee: APT Avant-Garde Technologies Date of Application: 02/02/95

Title:

PROCESS FOR MANUFACTURING MEDICATED CHEWING GUM WITH PLEASANT TASTE
INDEPENDENTLY OF THE ACTIVE PRINCIPLE ADDED AND CHEWING GUM TABLETS
OBTAINED

Desc.:

A process for producing medicated chewing gum with a pleasant flavor even when the active ingredient has an unpleasant taste and the chewing gum tablets so produced are claimed. The active ingredient is included in crystalline beta-cyclodextrin, dried, mixed with gum base and excipients and the medicated tablet is produced by cold pressing. The tablets may be made with sucrose and glucose or with sorbitol and high intensity sweeteners. Fillers may also be added. Active ingredients include vitamin C, paracetamol, ibuprofen and dimenhydrinate.

Key Words:

10 CHEWING GUM
16 Novelty (Gum)
25 Pharmaceutical
50 LOW INTENSITY SWEETENERS
150 HIGH INTENSITY SWEETENERS
361 Fillers
467 Pharmaceutical Agents
468 Dextrin,Cyclodextrin
478 Vitamins
504 Mixing/Gum Manufacture
515 Tableting
525 Chemical Synthesis/Preparation
555 Fast or Slow Release/Long Lasting
558 Sweetness Quality/Bitterness Supression
574 Health Benefit
579 Flavor Improvement
799 Other Company/Institution
821 Italy